Published in final edited form as:

Sleep Health. 2016 March ; 2(1): 63–68. doi:10.1016/j.sleh.2015.11.004.

Short-Term Moderate Sleep Restriction Decreases Insulin Sensitivity in Young Healthy Adults

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Abstract

Context and Purpose—The literature suggests that severe sleep loss of more than a few hours a night decreases glucose tolerance and insulin sensitivity. The aim of this study was to determine whether moderate sleep restriction had similar effects.

Methods—Fifteen healthy non-obese ($BMI=24.5\pm3.4$ kg/m²) young adults (20.6 ± 1.3 years) completed two 2-hour oral glucose tolerance tests (OGTT): one was after 3 days of time-in-bed restriction by 1–3 hours each night, and the other was after 3 days of ad libitum sleep. Glucose and insulin concentrations during OGTT, and fasting glucagon and cortisol concentrations were determined. The homeostasis model of insulin resistance (HOMA-IR), Matsuda index, and the quantitative insulin sensitivity check index (QUICKI) were calculated.

Results—The total time-in-bed during the sleep restriction and the ad libitum phase was 5.98 ± 0.76 and 7.98 ± 0.54 hours/day, and total sleep time was 5.16 ± 0.49 and 6.65 ± 0.64 hours/day, respectively. Glucose concentrations before and 30, 60, 90, and 120 minutes following consumption of glucose and area under the curve were not different for the two OGTT ($p > 0.10$ for all). Insulin concentration at fasting and area under the curve during the OGTT were significantly higher ($p = 0.034$ and 0.038 , respectively) following restricted sleep than following ad libitum sleep. Fasting glucagon concentration was also higher ($p = 0.003$). The HOMA-IR, Matsuda index, and QUICKI all suggested decreased insulin sensitivity following restricted sleep.

Conclusion—Short-term moderate sleep restriction reduced insulin sensitivity compared to ad libitum sleep in this group of healthy young adults.

Keywords

sleep duration; insulin sensitivity; glucose tolerance; chronic

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Authors' Contributions

XW designed the study, obtained funding, supervised the study, analyzed and interpreted data, and drafted the manuscript; JG obtained funding, acquired data, and reviewed the manuscript; RRP and KK acquired data and reviewed the manuscript; SDY helped design the study, interpreted the data and reviewed the manuscript. All authors approved the final version.

INTRODUCTION

Type 2 diabetes and its complications represent a significant and increasing public health burden. In recent years, there has been an increased interest in the potential role of insufficient sleep in the development of type 2 diabetes. An association between self-reported short sleep (<6 hours/day) and impaired glucose tolerance and diabetes has been shown by epidemiological data (1–9). Type 2 diabetes is characterized by reduced insulin sensitivity, and insulin-resistant individuals have been found to have fewer hours of sleep than insulin-sensitive individuals (10). Previous experimental studies have also shown that a range of sleep deprivation from one to a few nights of 4–5 h of sleep (11–17), to complete deprivation (18, 19) negatively affects glucose metabolism, reduces glucose tolerance or whole-body and adipose tissue insulin sensitivity. The relatively severe sleep restriction limits the generalization of these study findings.

The effects of sleep restriction of smaller degrees on glucose metabolism and insulin sensitivity have been investigated less. Of the few studies that examined smaller degree of insufficient sleep, one study found that two weeks of 5.5 h of sleep reduced glucose tolerance and insulin sensitivity compared to 8.5 h of sleep (20). High caloric intake was used in the study, which might confound their results. In another study, sleep restriction of 1.4 h for 8 weeks did not change glucose tolerance; however, the study was conducted in long sleepers (normal sleep duration > 8.5 h per night) (21). Given the U-shaped curve between sleep duration and diabetes shown in epidemiological studies (22, 23), results from studies of long sleepers likely are different from the effects of sleep restriction in individuals who are not long sleepers but go through periods of insufficient sleep (24).

In real-life situations, it is not unusual for an individual to adopt shortened sleep during the work week and to sleep more during the weekends. The National Sleep Foundation survey found that 25% of the sample self-reported not getting enough sleep during the weekdays and more than 40% reported sleeping longer during the weekend (25). A recent study found that three nights of sleep extension (10 hours) compared to sustained sleep restriction (6 hours) improved insulin sensitivity in young men (26). However, the 10-hour sleep duration seems to be longer than normal sleep duration even if it is used to “catch up” on sleep, and sleep extension may have its unique metabolic effects. In fact, 10-hour or more sleep was used as the control condition in a few of the aforementioned sleep restriction studies (12, 13, 17). In addition, individuals may require different amount of optimal sleep duration, and most previous studies used the same amount of time-in-bed for all participants. Therefore, the purpose of our study was to determine whether moderate sleep restriction of less than 3 hours per night affects glucose metabolism and insulin sensitivity compared to ad libitum sleep, by using oral glucose tolerance tests following 3 nights of reduced time-in-bed and 3 nights of ad libitum sleep. The secondary purpose of our study was to explore whether hormones involved in the regulation of glucose metabolism might change with sleep restriction.

METHODS

Participants

Sixteen young adults, aged 18–25 years, volunteered for the study. Each participant completed a medical history form and the Pittsburgh Sleep Quality Index (PSQI) which assesses sleep quality and disturbances during the past month (27). The exclusion criteria included: self-reported major health issues, taking sleep aid medication, using a sleep device, self-reported sleep problems such as apnea, insomnia, self-reported sleep duration of less than 6.5 hours or greater than 10 hours per day including naps during the day, and travel crossing time zones within one month of the study visits. One male had needle phobia and discontinued. Among the remaining 8 females and 7 males, there were 13 Non-Hispanic White, 1 African-American, and 1 Hispanic-White participants. All participants signed an informed consent approved by the University of South Carolina Institutional Review Board. This study was registered at clinicaltrials.gov (identifier: NCT02583750).

Procedures

Fifteen participants completed one oral glucose tolerance test (OGTT) after 3-day sleep restriction and another OGTT after 3-day ad libitum sleep within two weeks. The OGTTs were conducted in our research laboratory and during other time, they maintained their routine in their usual environment. Participants were told that we did not know what the study results would be. They were instructed to be careful to avoid driving and using hazardous things such as heavy machines while participating in the study.

The sequence of the phases was randomized. Six participants completed the sleep restriction phase first and the other nine participants completed the ad libitum sleep first. During the sleep restriction phase, participants were prescribed a range of times going to bed later and/or getting up earlier in order to reduce their time-in-bed by 1–3 hours based on their self-reported information in the PSQI. They were allowed to have various durations of time-in-bed for the three consecutive nights and they could choose how much to restrict their time-in-bed for each of the nights, but were asked to be in 1–3 hour window.

During the ad libitum sleep phase, participants were instructed to sleep as much as they wished for three consecutive nights. They were asked to maintain their usual napping habits, diet, caffeine usage, and daily activities during both sleep restriction and ad libitum sleep phases.

The participants wore an actigraph monitor (ActiGraph GT3X+, ActiGraph, Pensacola, FL) on their non-dominant wrist throughout the two phases. The output from the monitors was analyzed using the manufacturer provided software ActiLife 6.9. The Sadeh algorithm (Sadeh) (28) was used to determine minute-by-minute asleep/awake status. Total sleep time was the total number of minutes scored as “asleep”. They also recorded the time they went to bed, got up, and took naps during those days. Total time-in-bed was the total time from going into bed to getting up plus any naps during the day recorded by participants.

During the day after the third night of each phase, following an overnight fast of at least 12 hours, participants arrived at our research laboratory between 0700 and 1000 hour. Height

and weight were measured with shoes and outer garments removed, and an oral glucose tolerance test (OGTT) was performed. A 20-gauge polyethylene catheter was placed in an antecubital vein for blood sampling. Blood samples were collected before (0 min) and 30, 60, 90, and 120 min after consuming a 75-g glucose drink. An Epworth Sleepiness Scale (29) was also completed during this visit. The score for the scale ranges from 0 to 24, with higher scores indicating greater sleepiness.

Plasma glucose was measured immediately using a glucose analyzer (YSI 2300, YSI Inc., Ohio). Other blood samples were collected using heparin-treated evacuated tubes. Samples were spun and plasma was separated and stored at -80°C until final analysis. Plasma insulin concentrations at 0, 30, 60, 90, and 120 min during the OGTT, and fasting plasma cortisol concentrations were measured by enzyme-linked immunosorbent assay following manufacturer's instructions (EMD Millipore, St. Charles, MO). Fasting plasma glucagon concentrations were measured by chemiluminescent ELISA assay (EMD Millipore, St. Charles, MO).

Calculations

Glucose and insulin areas under the curve (AUC) were calculated using the trapezoid rule: $\frac{1}{2} \times 30 \times (y_{0\text{min}} + 2y_{30\text{min}} + 2y_{60\text{min}} + 2y_{90\text{min}} + y_{120\text{min}})$, where y represents glucose or insulin concentration at the different time points (30). Homeostasis model of insulin resistance (HOMA-IR) was calculated as the product of fasting glucose concentration ($G(0)$) in mg/dL and fasting insulin concentration ($I(0)$) in mU/L divided by 405 (31). The quantitative insulin sensitivity check index (QUICKI) was calculated as $1/[\log(I(0)) + \log(G(0))]$ (32). The Matsuda index was calculated as $(10,000/\text{square root of } [G(0) \times I(0)] \times [\text{mean glucose} \times \text{mean insulin during OGTT}])$ (33).

Statistics

Data were analyzed using IBM SPSS Statistics version 20 (IBM Corp.). The outcome variables included concentrations of glucose, insulin, glucagon, and cortisol, and glucose and insulin AUC, as well as calculated insulin resistance/sensitivity indices (HOMA-IR, QUICKI, and Matsuda). Descriptive statistics were calculated. For non-normally distributed variables, data are presented as median and quartiles and transformed to achieve normality of distribution for analysis. Analyses of Variance with repeated measures were performed to compare outcome variables obtained from the two OGTTs with data from the same individual analyzed as paired observations. Sex was included in the models initially in the analyses to determine if the comparison of the outcome variables between the two OGTTs were different by sex (sex by condition interaction). Because the sex by condition interaction was not significant for any outcome variable, we report combined data of male and female participants. Hedges' g effect size of the differences between means of HOMA-IR, QUICKI, and Matsuda indices obtained from the two OGTTs were calculated. Correlations (Pearson correlations for normally distributed variables and Spearman correlations for non-normally distributed variables) between the changes between the two conditions in time-in-bed, total sleep time, with changes in glucose and insulin AUC, and insulin resistance indices were calculated. A p value of <0.05 was considered statistically significant.

RESULTS

The participants were young (20.6 ± 1.3 years, mean $\pm$ SD), non-obese (body mass index = 24.5 ± 3.4 kg/m²). The participants' baseline PSQI global score was 4.3 ± 1.6 , reflecting good sleep quality in general. The self-reported usual sleep duration was 7.43 ± 0.64 hours/day. The self-reported total time-in-bed (including naps during the day) during the sleep restriction phase and the ad libitum phase was 5.98 ± 0.76 and 7.98 ± 0.54 hours/day, respectively, reflecting a difference of 2.00 ± 0.54 hours/day between the conditions (range: 0.9–3.2 hours/day) (Table 1). The total sleep time estimated by actigraph during the sleep restriction phase and ad libitum sleep was 5.16 ± 0.49 and 6.65 ± 0.64 hours/day, respectively, reflecting a difference of 1.45 ± 0.59 hours/day (range: 0.5–2.6 hours/day). Consequently, the score for the Epworth Sleepiness Scale after three days of sleep restriction was significantly higher than after ad libitum sleep (9.9 ± 4.0 and 3.8 ± 2.2 , respectively, $p < 0.001$).

Body weight in the mornings prior to the OGTT tests was similar ($p = 0.80$) following sleep restriction (74.2 ± 13.4 kg) and following ad libitum sleep (74.2 ± 13.2 kg) (Table 1). Plasma concentrations of glucose and insulin before and 30, 60, 90, and 120 minutes following consumption of the glucose drink during the OGTT are shown in Figures 1 and 2, respectively. As shown in Figure 1A, at all the time points there were no differences in glucose concentrations between the sleep restriction and ad libitum sleep conditions ($p > 0.10$ for all). The glucose AUC was also similar (12976 ± 2298 and 12258 ± 2593 mg/dL•2h, respectively, $p = 0.91$).

Insulin concentrations before consumption of glucose drink was significantly higher ($p = 0.034$) following sleep restriction than following ad libitum sleep. At 30 and 90 minutes following consumption of the glucose drink, insulin concentrations tended to be higher following sleep restriction than following ad libitum sleep ($p = 0.060$ and 0.068 , respectively). At 60 and 120 minutes, insulin concentrations were not statistically different ($p > 0.10$ for both). The insulin AUC (Figure 1B) for the OGTT following sleep restriction was approximately 20% higher than following ad libitum sleep (3012 ± 1596 and 2516 ± 1371 μ U/ml•2h, respectively, $p = 0.037$), suggesting significantly greater amount of insulin was secreted in response to the glucose challenge.

Table 1 includes the calculated insulin resistance/sensitivity indices. Following sleep restriction, the Matsuda index was significantly lower ($p = 0.014$) than following ad libitum sleep. There were also trends for a significantly greater HOMA-IR ($p = 0.057$) and a significantly lower QUICKI ($p = 0.052$). All three indices suggest lower insulin sensitivity following sleep restriction. The Hedges' g for Matsuda index, HOMA-IR, and QUICKI was 0.45, 0.45, and 0.53, respectively, representing medium effect sizes.

Also included in Table 1 are fasting plasma concentrations of glucagon, and cortisol following restricted sleep and ad libitum sleep. Glucagon concentration was significantly higher ($p = 0.003$) following restricted sleep than ad libitum sleep. Cortisol concentrations were not different following the two conditions.

In order to account for the different degree of sleep restriction, the comparison between the sleep restriction and ad libitum conditions were also conducted with adjustment for

differences in total sleep time between the two conditions. Most of above findings remained (fasting insulin $p=0.048$; insulin concentration at 90 minutes $p=0.018$; insulin AUC $p=0.025$; Matsuda index $p=0.067$; QUICK index $p=0.075$; HOMA-IR $p=0.047$). There were no significant correlations between changes in time-in-bed (Spearman correlations) or total sleep time (Pearson correlations) between the two conditions with changes in insulin concentrations, insulin sensitivity indices, and glucagon concentrations (p values > 0.05).

Additionally, sleep duration during sleep restriction and ad libitum conditions did not vary by the order of sleep conditions (sleep restriction before and after ad libitum sleep, $p > 0.60$ for all). When the interaction of sleep condition by order was included in the Analyses of Variance with repeated measures models, the interaction was not significant for outcome variables ($p > 0.05$ for all).

DISCUSSION

The primary findings of this study were that following three nights of time-in-bed restriction ranging from less than an hour to three hours, there was a range of changes related to insulin sensitivity. The changes included an increase in insulin concentrations at fasting and during the OGTT, and a higher fasting plasma glucagon concentration. Also, the changes in the calculated HOMA-IR, Matsuda, and QUICKI indices suggest decreased insulin sensitivity. Together, these results suggest that the three nights of mild-moderate sleep restriction reduced insulin sensitivity in these young healthy adults. The metabolic system was able to maintain glucose homeostasis by changing hormonal secretion; however, the body may be at a metabolically challenged state during moderate sleep restriction. Whether repeated challenges of chronic insufficient sleep may contribute to the development of type 2 diabetes needs further investigation.

Our study and a few others (11, 13, 34, 35) did not find any change in glucose concentration by sleep restriction during fasting state. We also did not observe a difference in post-glucose challenge plasma glucose concentrations when sleep duration was reduced. However, one study using continuous glucose monitoring found interstitial glucose concentrations were higher after meals and during the night-time period when sleep was restricted to 4 hours for 5 nights (13). Another study (12), using a frequently sampled intravenous glucose tolerance test found that glucose clearance after injection of glucose was slower after 6 nights of 4-hour sleep. The study by Nedeltcheva et al. showed higher 2-hour glucose concentration during OGTT with 5.5-hour sleep for 14 days vs. 8.5-hour sleep (20). A recent study found higher glucose AUC during OGTT after 3 nights of 6-hour sleep compared to 10-hour sleep (26). Compared to these studies, our study was of either shorter duration (3 nights) or smaller degree of sleep restriction.

The present finding of greater insulin concentrations at fasting, 30 min, and 90 min (a trend), as well as greater AUC when sleep was restricted, was consistent with some studies (13, 19) but not others (11, 20). Of the two studies that did not show changed insulin concentrations, one was after a single night of 4-hour sleep (11) and the other was 14 days of sleep restriction (20). Despite these differences, our finding that sleep restriction reduces insulin sensitivity was consistent with earlier studies with more severe sleep loss (11, 18, 19) or

more days of sleep restriction(17, 20). The fact that all three insulin resistance/sensitivity indices showed significant (or tendency toward) differences between restricted and ad libitum sleep conditions reinforces the conclusion that insulin sensitivity was reduced by sleep restriction. The variances in study findings in regard to glucose and insulin concentrations may be related to the degree and number of days of sleep restriction, and the participants' characteristics.

These results are in contrast with sleep restriction studies conducted in long sleepers (>8.5 hour), which did not find a difference in insulin sensitivity with time-in-bed restriction (21). There are two issues to be considered in this contrast. First, restricting sleep duration in long sleepers may move the sleep duration toward the optimal range, given the U-shaped association between sleep duration and diabetes (22, 23). Second, the sleep restriction in long sleepers in that study was an 8-week intervention, whereas the present and other studies involved sleep restriction for just a few days. Another study in individuals whose typical sleep was 7–7.5 hours showed that insulin sensitivity decreased after 1-week sleep restriction for 1.5 hours but returned to baseline after two additional weeks (36). Thus, it is possible that there are compensatory mechanisms which occur with more chronic sleep restriction.

As with other studies, morning cortisol concentrations did not change with sleep restriction (12, 13, 20, 26, 37, 38). Evening cortisol concentration, when it is usually low, has been found to elevate following sleep restriction in other studies (12, 13, 17, 20, 37–40). In our study, we showed increased fasting glucagon concentrations with sleep restriction. Previously, reduced glucagon concentrations (35) were reported after one night of 4.5-hour sleep. In that study, fasting glucose and insulin concentrations were unchanged. Yet, another study by Donga et al.(11) did not find any difference in glucagon concentration with one night of 4-hour sleep. In their study, fasting glucose and insulin concentrations did not change either. Therefore, the changes in glucagon together with increased insulin concentrations found in our study, might reflect simultaneous changes to maintain glucose homeostasis.

It may be inevitable to have shortened sleep at times. In interpreting our results, it should be noted that with three nights of ad libitum sleep, insulin sensitivity was better than that following sleep restriction. These results are in agreement with the recent study by Killick et al (26), in which insulin sensitivity was higher following three nights of sleep extension compared to sustained sleep restriction. In that study, sleep extension (10-hour sleep) was used instead of ad libitum sleep as we adopted in our study. Of note, a few other aforementioned sleep restriction studies also compared with 10-hour or more sleep which is longer than a typical duration of sleep (12, 13, 17). In our study, the ad libitum sleep duration was still slightly shorter than a typical sleep duration as they reported and the mean difference in sleep duration between restricted and ad libitum conditions were approximately one and a half hour. Therefore, results of our study suggest that as little as one and a half hour less of sleep could have metabolic consequences.

We suspect the mechanisms for the reduced insulin sensitivity likely involves multiple pathways. There is evidence showing impaired insulin signaling in human adipocytes and

elevated circulating free fatty acid concentration after 4 days of 4.5 hours in bed as compared to 8.5 hours in bed (41, 42). Also, inadequate pancreatic beta cell responsivity was found after prolonged (3 weeks of 5.6 hours sleep/24 hour) sleep restriction with concurrent circadian disruption (43). Heart rate variability recording supported a shift toward higher sympathovagal balance after 6 days of 4 hour bedtime (44). However, another study did not find association between changes in insulin sensitivity and changes in hypothalamic-pituitary-adrenal axis function and sympathetic nervous system function after 7 nights of 5 hour/night in bed, compared with 10 hour/night in bed for 8 nights (17). Additionally, disturbance of hormonal secretion, such as cortisol and growth hormone, may also contribute. These studies suggest involvement of multiple pathways in the regulation of insulin sensitivity; however, the sleep restriction was to a greater extent and the number of days was more than in our study. The effects of short-term mild-moderate sleep restriction may be different, but our study could not determine the exact mechanism.

Our participants were young and healthy. Given the results, it would be important to determine whether sleep restriction has similar unfavorable effects on individuals who already have impaired glucose tolerance and who may be unable to compensate metabolically to maintain glucose homeostasis. Secondly, the restricted sleep period was three nights. Therefore, we were unable to determine if the findings were due to the last night of sleep restriction or they were accumulative effects of three nights. Conversely, we were unable to determine whether one night of ad libitum sleep was “enough” to reverse the harmful effects on insulin sensitivity, or more than one night would be needed to counteract the effects of sleep restriction. Therefore, it would be of public health interest to determine whether the pattern of chronic shorted sleep during the workweek coupled with “catching up” on sleep during the weekend, in the long run, is harmful, and whether consistently sufficient sleep is needed to maintain metabolic health. More prolonged interventions are needed to establish whether these effects accumulate or whether there are compensatory responses.

In addition, participants self-reported their time-in-bed in our study. Although this may be prone to be inaccurate like any self-reported information, the information was consistent with that recorded by the actigraph. We also did not monitor their dietary intake or physical activity but only instructed them to maintain their usual diet and physical activity during the experimental days, which could affect some results. Lastly, considering the duration of sleep needed by each individual is different, we prescribed sleep restriction based on each individual’s typical sleep duration rather than using a uniform sleep duration. We also allowed participants flexibility to choose the amount of sleep restriction (within 1–3 hours) based on how they felt on any of the three days. This approach reduces the safety concern of conducting sleep restriction intervention outside the laboratory, and it may also be closer to the real life where individuals vary sleep duration based on how they feel.

In summary, this study showed that three consecutive nights of sleep restriction reduced insulin sensitivity compared to ad libitum sleep in young healthy participants. Future studies are needed to determine the effects of mild to moderate chronic sleep restriction and periodic “catching up” on sleep, as well as to conduct studies in individuals with impaired glucose tolerance.

Acknowledgments

The authors would like to dedicate this work to Dr. Raja Fayad, who has contributed significantly to this work but passed away before the completion of this manuscript.

Sources of Support: This work was supported by University of South Carolina Magellan Scholar Award (X.W.), American Heart Association grant 14BGIA20380706 (X.W.), and R01-HL095799 (S.D.Y.). J.G. was supported by Magellan Mini-Grant and Magellan Apprentice award. X.W. received salary support from NIH grant R00AG031297.

Abbreviations

OGTT	oral glucose tolerance test
HOMA-IR	homeostasis model of insulin resistance
QUICKI	quantitative insulin sensitivity check index
AUC	area under the curve

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Figure 1A.

Glucose concentrations during oral glucose tolerance tests (n=15). Data are means $\pm$ SE.

Figure 1B.

Insulin concentrations during oral glucose tolerance tests (n=15). The area under the curve for the oral glucose tolerance test following sleep restriction was higher than that following ad libitum sleep ($p = 0.037$). Data are means $\pm$ SE.

Table 1

Comparison of time-in-bed, total sleep time, weight, calculated insulin sensitivity/resistance indices, and fasting plasma glucagon and cortisol concentrations following restricted sleep and ad libitum sleep

Index	Restricted sleep	Ad libitum sleep	P value
Time-in-bed *, h	5.98±0.76	7.98±0.54	<0.001
Total sleep time †, h	5.16±0.49	6.65±0.64	<0.001
Body weight, kg	74.2±13.4	74.2±13.2	0.80
HOMA IR	0.82±0.35	0.67±0.31	0.057
QUICK I	0.40±0.03	0.42±0.03	0.052
Matsuda	14.1±6.2	17.6±8.8	0.014
Glucagon, pg/ml	6.5 (5.6, 10.2)	3.8 (3.3, 4.6)	0.003‡
Cortisol, ng/ml	227±84	212±113	0.60

Values are mean±SD or median (quartiles).

* self-reported;

† estimated by actigraph;

‡ p value is on log-transformed data.